

Breath Holding Spells: Evaluation of Autonomic Nervous System Function

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This study attempted to determine noninvasively whether a dysregulation of autonomic reflexes exists in children with breath holding spells (BHS). Fifty children between 13 to 47 months of age who had experienced BHS were evaluated at a time when they stopped having spells, for autonomic nervous system (ANS) dysfunction. The results were compared with the test results of control group of 100 normal children (age and sex matched). Breath holding children displayed significantly high resting heart rate and resting diastolic BP ($P < 0.001$): significantly abnormal 30:15 R-R ratio after rising from supine to standing position ($P < 0.001$): showed significant hypersensitivity of pupil on instillation of 0.125% pilocarpine into conjunctival sac ($P < 0.001$): and positive "Orthostatic signs" when compared to control group ($P < 0.001$). This study correlates with the hypothesis that a subtle underlying generalized autonomic dysfunction exists in children with BHS.

Key words: *Autonomic nervous system, Breath holding spells.*

BREATH holding spells (BHS) are dramatic, involuntary episodes that occur in otherwise healthy children. These episodes are often frightening to parents until the situation is 'defused' by explanation and reassurance. The attacks are self limited and usually outgrown by school age. Breath holding spells are a well-recognized common problem. Childhood breath holding conjures up an image of a stubborn toddler willfully holding his breath until he gets what he wants. However the reality is quite different. Kohyama, *et al.*(1) and Kahn, *et al.*(2), have hypothesized that functional brainstem disturbances and immature breathing control are involved in the occurrence of breath-holding spells. Many others have reported an association of iron deficiency anemia with breath-holding spells and improvement with

iron therapy(3-6). Recently, DiMario in his studies has shown that there was generalized autonomic dysfunction in children with BHS(7,8), which has created lot of interest in other researchers. This dysregulation may contribute for the pathophysiology of severe BHS in these children. This, study was undertaken to determine non-invasively whether a dysregulation of autonomic nervous system exists in children with BHS.

Subjects and Methods

This descriptive study was done in the Child Guidance Clinic, Institute of Child Health and Hospital for Children, Chennai, during November 2002 to October 2003. The study population included all children between 13 to 47 months age group, diagnosed clinically to have breath holding spells (based

on history given by their parents or by observation of spells). Spells were defined as the child's breathing stopping in expiration after a deep inspiration during crying. Only those children who are able to stand independently are included in this study. Age, sex and weight matched children, who never had BHS previously were included as controls. These are children attending out patient department for minor ailments. Children with primary cardiac disease and primary central nervous system disease were excluded from this study. A total of 50 children with breath holding spells and 100 children without BHS were studied. All children were registered for the study after taking consent from the parents or guardians. All children were evaluated according to a standard protocol. Detailed pre and postnatal history, information about breath holding spells (type of spells, age of onset, frequency duration of each episode, usual triggering factors, associated convulsion and its type), associated behavioral problems, developmental history and information on breath holding spells in any first degree family member were recorded. Complete general and physical examination was done in each child. Hemoglobin estimation was done in all cases by Sahli's method. Autonomic nervous system function was tested in all children in the following manner.

Sympathetic Cardiovascular Reflex Tests

Postural fall in BP: The BP of the child was recorded in lying posture and then on standing for at least 3 minutes. The postural fall of systolic, diastolic blood pressures and that of mean arterial pressure was noted. Blood pressure was measured using an automated NIBP monitor. Sustained drop in systolic (>20mm Hg) and diastolic (>10mm Hg) blood pressure unassociated with an appropriate increase in heart rate are suggestive of an autonomic deficit(10).

Pilocarpine Eye Test

This test is based on the principle of cholinergic super sensitivity of sphincter in patients with familial dysautonomia. This is a nonspecific sign of parasympathetic denervation. Pilocarpine produces miosis in patients with autonomic dysfunction but no detectable effect in normal children(11). 0.125% pilocarpine was instilled into the conjunctival sac of one eye of the patient. The other eye served as control. Pupillary size before and after instillation of pilocarpine into conjunctival sac was measured using Kestenbaum scale. The pupils were compared after 5 minutes.

All the tests (procedures) were repeated thrice and the average of the three values was taken for the study. All children with breath holding spells were counseled at the child guidance clinic of our hospital. Parents were explained about the benign nature of the breath holding spells and that children will outgrow this problem. All cases of BHS with hemoglobin concentration less than 10.5 g/dL were given iron (ferrous sulfate) 6 mg/kg/d and followed up once in two weeks.

Statistical analysis was done using SPSS 10 and EPI info software. For qualitative data, Pearson Chi-square tests were employed. For comparison of quantitative data of two groups, students 't' was used. Analysis of variance "F test" was used when more than two groups were compared.

Results

Total number of children with breath holding spells included in the study was 50. Maximum number (60%) of cases was found in the age group of 1-2 years. Male to female ratio was 3:2 and the male predominance was seen in all the age groups. Most common age of onset of BHS was between the ages 7-12 m(50%). By 18 m about 43 (86%) cases had

TABLE I—Basal Heart Rate and Blood Pressure in Children with and without Breath-Holding Spells.

Parameters	Cases		Controls		P value
	Mean	(SD)	Mean	(SD)	
Basal HR (per min)	103.40	(10.07)	87.52	(10.64)	0.001
SBP (mm Hg)	103.86	(8.91)	90.29	(9.82)	0.175
DBP (mm Hg)	65.0	(9.44)	55.83	(8.87)	0.001
MAP (mm Hg)	74.98	(8.65)	72.65	(10.33)	0.169

BHS: Breath holding spells. HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure.

their first episode of BHS and by 24 m, 49 (98%) cases had their first episode of BHS. The mean age of onset was 13.22 (range 13-47 months). Mean frequency observed was 3.8 (1.44)/wk. The minimum frequency was once per month and maximum was 7 episodes per day. 47 (94%) had cyanotic breath holding spells. Only 3 (6%) had pallid breath-holding spells. Mean hemoglobin in the study group was 8.86 (1.44) g/dL as compared to 10.02 (1.37 g/dL in the control group, the difference was statistically significant ($P = 0.001$). Mean Hb concentration was lower in children with higher frequency of BHS, (<1/week 9.08 g/dL; 1-3/week 8.62 g/dL; >3/week 8.22 g/dL) but the difference was not significant ($P = 0.155$).

Evaluation of Autonomic Nervous System Function

The mean basal heart rate [103.40 (10.07) per min] in the study group was higher when compared to that of control group [87.52 (10.64) per min] ($P = 0.001$). The basal systolic, and mean blood pressures were high in the study group when compared to the control group. But only diastolic blood pressure difference between the study and the control group was statistically significant ($P = 0.001$) (Table I). Among the study group, 10 (20%) children showed 30:15 R-R ratio <1; 16 (32%) children showed 30:15 R-R ratio

between 1.01-1.03 and 24 (48%) had 30:15 R-R ratio >1.04. Among the controls, 34% had 30:15 R-R ratio between 1.01-1.03 and rest (66%) had 30:15 R-R ratio >1.04, difference was statistically significant ($P = 0.001$). Fourteen (28%) out of 50 children with BHS showed papillary constriction on instillation of 0.125% pilocarpine into conjunctival sac as compared to 6 (6%) children among control group. The difference between the two groups was significant ($P = 0.001$) (Table II). More number of study group children *i.e.*, 26 (52%) had >20 mm H₂ fall in SBP after standing compared to 10 (10%) among the control group ($P = 0.001$). Among the study group, 37 (74%) showed >10 mm Hg fall in DBP upon standing compared to 29 (%) among the control group. The difference between the two groups was statistically significant ($P = 0.001$). Among children with BHS, 38 (76%) showed >10 mm Hg fall MAP on standing compared to 27% among the control group ($P = 0.001$) (Table III).

Discussion

In the present study, the basal HR and resting diastolic blood pressure in cases were significantly high in comparison to that of controls. Twenty six (52%) children among the cases showed unsustained increase in heart rate during the lying to standing maneuver. Twenty-six (52%) showed >20mm Hg fall in

TABLE II—Interval Ratio on Standing and Pilocarpine Eye Test.

R-R Ratio	Cases n(%)	Control n(%)
> 1.04	24 (48)	66 (66)
1.01 - 1.03	16 (32)	34 (34)
<1	10 (20)	Nil
	<i>P</i> = 0.001	
<i>Pupillary Reaction</i>		
No response	36 (72)	94 (94)
Constriction	14 (28)	6 (6)
	<i>P</i> < 0.001	

BHS: Breath holding spells

SBP, thirty-seven (73%) had a 10mm Hg fall in DBP and thirty-eight (76%) had >10 mm Hg fall in mean arterial pressure indicating positive orthostatic signs. Among 50 cases, significant number (28%) of children showed constriction of pupil after instillation of 0.125% pilocarpine when compared to controls. These results indicate that children with BHS have underlying autonomic nervous system dysregulation. Similar results were reported by other studies(7,8).

In the study by DiMario, *et al.*(7) five children with pallid BHS (PBHS) were evaluated at a time when they were clear of spells for ANS dysfunction. Breath-holders displayed a significant percent decrease in mean arterial pressure and an unsustained increase in pulse rate during the lying to standing maneuver, two children with PBHS had “positive orthostatic signs”, and one child with PBHS had a plasma norepinephrine level of 94 pg/mL (60% below the mean)(7).

DiMario *et al*(8) demonstrated in the cyanotic BHS group a significantly greater increase in pulse rate after rising from the supine position with a trend toward a concomitant higher mean arterial pressure.

TABLE III—Postural BP Changes Among Children.

	Cases	Controls
Decrease in SBP (mm Hg)		
<20	24 (48)	90 (90)
>20	26 (52)	10 (10)
	<i>P</i> < 0.001	
Decrease in DBP (mm Hg)		
<10	13 (26)	71 (71)
>10	37 (74)	29 (29)
	<i>P</i> = 0.001	
Decrease in MAP (mm Hg)		
<10 mm Hg	12 (24)	73 (73)
>10 mm Hg	38 (76)	27 (27)
	<i>P</i> = 0.001	

BHS: Breath holding spells. SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure.

After adjusting for age, sex and mean supine systolic and diastolic blood pressures, breath-holders had greater decreases in diastolic blood pressure without an increase in systolic blood pressure after standing from the supine position. Breath-holders also had significantly abnormal 30:15 R-R interval ratios compared with controls.

In two other studies by DiMario, *et al.*, investigated centrally mediated parasympathetic regulation of modulated cardiac vagal tone among children with severe cyanotic and pallid breath-holding spells by examining respiratory sinus arrhythmia(12,13).

Our observations show clear evidence of autonomic nervous system dysfunction in breath-holding spells as suggested by high resting heart rate and diastolic blood pressure, abnormal 30:15 R-R ratio when rising from supine position, as well as other orthostatic signs like decrease in systolic, diastolic and mean blood pressure and hyper sensitivity of the pupil to pilocarpine instillation.

Contributors: BGA conceptualizations of research,

Key Messages

- Autonomic nervous system dysregulation is observed in children with breath holding spell.
- Children with breath holding spells have significantly lower hemoglobin when compared to children without BHS.

preparation of the protocol, clinical data collection, review of literature and drafting of the manuscript, shall act as the guarantor; KN designing of the study, critical appraisal of protocol, supervision and monitoring of data collection, interpretation of data and helped in drafting the manuscript; VJ conceptualization of research, review of literature, critical revision of the manuscript for important intellectual content; MP helped in analysis and final draft of the manuscript.

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